$%^Other;HighlightOn=**;HighlightOff=**;
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FILE 'USPAT' ENTERED AT 16:55:37 ON 08 OCT 1997

 ************************************
 *        WELCOME TO THE            *
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 ************************************

=> s shigella
L1       1802 SHIGELLA

=> s mammal?
L2      39731 MAMMAL?

=> s l1(p)l2
L3         92 L1(P)L2

=> s entry or enter or entered
      146491 ENTRY
      212429 ENTER
       85752 ENTERED
L4    348306 ENTRY OR ENTER OR ENTERED

=> s l4(p)l3
L5          1 L4(P)L3

=> d

1. 5,663,317, Sep. 2, 1997, Microorganism having attenuated
invasiveness; Stanley Falkow, et al., 536/23.7; 935/9, 11 :IMAGE
AVAILABLE:

=> d ab

US PAT NO:     5,663,317 :IMAGE AVAILABLE:          L5: 1 of 1

ABSTRACT:

 The invention provides nucleic acids encoding one or more hyper-invasive
genes within the hil locus (hyper-invasion locus) or fragments thereof,
methods for making attenuated microorganisms and identifying such
hyper-invasive nucleic acids as well as mutant microorganisms wherein one
or more hyper-invasive genes within the hil locus are modified to
attenuate the invasive phenotype of the microorganism. The methods of the
invention utilize conditions which repress invasiveness in an otherwise
invasive microorganism. The method comprises mutating an invasive
microorganism to form a plurality of mutant microorganisms. The thus
formed mutants are exposed to conditions which repress invasiveness of
the parental invasive microorganism. At least one mutant microorganism is
then detected which exhibits an increase in invasiveness as compared to
the parental invasive microorganism. The site of mutation in the genome
of the mutant microorganism is then determined to localize and identify
one or more hyper-invasive genes within the hil locus of the invasive
microorganism.

=> s aspartate(4a)dehydrogenase
       2961 ASPARTATE
       5291 DEHYDROGENASE
L6      104 ASPARTATE(4A)DEHYDROGENASE

=> d his
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(FILE 'USPAT' ENTERED AT 16:55:37 ON 08 OCT 1997)
L1 1802 S SHIGELLA
L2 39731 S MAMMAL?
L3 92 S L1(P)L2
L4 348306 S ENTRY OR ENTER OR ENTERED
L5 1 S L4(P)L3
L6 104 S ASPARTATE(4A)DEHYDROGENASE

=> s l1(p)l6
L7 0 L1(P)L6

=> s l1 and l6
L8 4 L1 AND L6

=> d 1-4

1. 5,672,345, Sep. 30, 1997, Selective maintenance of a recombinant gene in a population of vaccine cells; Roy Curtiss, III, 424/93.2; 435/69.1, 71.2, 172.3, 252.3 :IMAGE AVAILABLE:

2. 5,595,889, Jan. 21, 1997, Process for integration of a chosen gene on the chromosome of a bacterium using Mu transposons; Fran.cedilla.ois Richaud, et al., 435/71.2, 69.1, 71.1, 172.3, 243, 252.3, 847, 849; 935/42, 52, 72, 73 :IMAGE AVAILABLE:

3. 5,387,744, Feb. 7, 1995, Avirulent microbes and uses therefor: Salmonella typhi; Roy Curtiss, III, et al., 424/235.1, 258.1; 435/172.3, 252.3, 252.33, 320.1, 879; 935/60, 62, 72 :IMAGE AVAILABLE:

4. 5,294,441, Mar. 15, 1994, Avirulent microbes and uses therefor: salmonella typhi; Roy Curtiss, III, 424/200.1, 235.1, 258.1; 435/172.3, 252.3, 252.33, 320.1, 879; 935/60, 62, 72 :IMAGE AVAILABLE:

=> d 1 ab

US PAT NO: 5,672,345 :IMAGE AVAILABLE: L8: 1 of 4

ABSTRACT:
The invention encompasses methods of maintaining desired recombinant genes in a genetic population of cells expressing the recombinant gene. The methods utilize mutant cells which are characterized by a lack of a functioning native gene encoding an enzyme which is essential for cell survival, wherein this enzyme catalyzes a step in the biosynthesis of an essential cell wall structural component and the presence of a first recombinant gene encoding an enzyme which is a functional replacement for the native enzyme, wherein the first recombinant gene cannot replace the defective chromosomal gene. The first recombinant gene is structurally linked to a second recombinant gene encoding a desired product. Loss of the first recombinant gene causes the cells to lyse when the cells are in an environment where a product due to the expression of the first recombinant gene is absent. The invention also encompasses methods of creating and isolating mutant cells with the above characteristics. The cells of the invention are useful for commercial production of desired products, for components of vaccines for immunizing individuals, and for release into the environment.

=> d 1 fd parn

US PAT NO: 5,672,345 :IMAGE AVAILABLE: L8: 1 of 4
DATE FILED: Mar. 10, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of application Ser. No. 07/990,361 filed Dec. 15, 1992, abandoned, which is a continuation of application Ser. No. 07/251,304 filed Oct. 3, 1988, abandoned which is a continuation-in-part of commonly owned application Ser. No. 07/106,072 filed Oct. 7, 1987, now abandoned.

=> d clms

US PAT NO: 5,672,345 :IMAGE AVAILABLE: L8: 1 of 4

CLAIMS:

CLMS(1)

I claim:

1. A live bacterial carrier for a vaccine for immunizing an individual, said carrier comprising an avirulent derivative of a pathogenic strain of bacteria characterized by:
a) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd);
b) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
c) the presence of a second recombinant gene encoding a desired polypeptide; and
d) physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival.

CLMS(2)

2. The live bacterial carrier according to claim 1 wherein said bacterial carrier is formulated in a pharmaceutically acceptable excipient in a pharmacologically effective dose.

CLMS(3)

3. The live bacterial carrier of claim 1, wherein the avirulent derivative of a pathogenic strain of bacteria is a Salmonella.

CLMS(4)

4. The live bacterial carrier of claim 3, wherein the first recombinant gene encodes Asd derived from Streptococcus mutans.

CLMS(5)

5. The live bacterial carrier of claim 4, wherein the second recombinant gene encodes an antigenic determinant encoded with the spaA gene of S. mutans.

CLMS(6)

6. The live bacterial carrier of claim 5, wherein the first recombinant gene encodes Asd derived from S. typhimurium.

CLMS(7)

7. A composition for stimulating an immune response in an individual comprising a live avirulent derivative of a pathogenic strain of bacteria characterized by:
a) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd);
b) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
c) the presence of a second recombinant gene encoding a desired polypeptide; and physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival.

CLMS(8)

8. The composition of claim 7, wherein the avirulent derivative of a pathogenic strain of bacteria is a Salmonella.

CLMS(9)

9. The composition of claim 8, wherein the first recombinant gene encodes Asd derived from S. mutans.

CLMS(10)

10. The composition of claim 9, wherein the second recombinant gene encodes an antigenic determinant encoded within a spaA gene of S. mutans.

CLMS(11)

11. The composition of claim 10, wherein the first recombinant gene encodes Asd dervied from S. typhimurium.

CLMS(12)

12. A method of immunizing an individual comprising administering the live bacterial carrier for a vaccine of claim 1 to the individual.

CLMS(13)

13. A method of stimulating the immune system of an individual comprising administering the composition of claim 7 to the individual.

CLMS(14)

14. A method of preparing a bacterial carrier for a vaccine for immunization of an individual, said method comprising:
a) providing an avirulent derivative of a pathogenic strain of bacteria characterized by:
1) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd)
2) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
3) the presence of a second recombinant gene encoding a desired polypeptide; and
4) physical linkage between the first recombinant gene and the second recombinant gene, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival;

b) providing a suitable excipient; and
c) mixing the bacteria with the excipient in a suitable pharmacologic dose.

CLMS(15)

15. An immunogenic composition comprising an avirulent derivative of a pathogenic strain of bacteria characterized by:
a) a lack of a functioning native chromosomal gene encoding a first enzyme which is a .beta.-aspartic semialdehyde dehydrogenase (Asd);
b) the presence of a first recombinant gene encoding a second Asd enzyme wherein the first recombinant gene cannot recombine to replace the defective chromosomal gene;
c) the presence of a second recombinant gene encoding a desired polypeptide; and
d) physical linkage between the first recombinant gene and the second recombinant gent, wherein loss of the first recombinant gene causes the bacteria to lyse when in an environment which requires expression of said first recombinant gene for cell survival.

CLMS(16)

16. The composition of claim 15 wherein the second recombinant gene encodes an antigenic determinant encoded within a spaA gene of S. mutans.

=> d kwic

US PAT NO: 5,672,345 :IMAGE AVAILABLE: L8: 1 of 4

SUMMARY:

BSUM(67)

Yet another aspect of the invention is a method of creating and isolating bacteria containing a mutation in a gene encoding beta-**aspartate** semialdehyde **dehydrogenase** (asd), comprising:

DETDESC:

DETD(6)

"Gram . . . rods. The genera of gram negative bacteria include, for example, Neisseria, Spirillum, Pasteurella, Brucella, Yersinia, Francisella, Haemophilus, Bordetella, Escherichia, Salmonella, **Shigella**, Klebsiella, Proteus, Vibrio, Pseudomonas, Bacteroides, Acetobacter, Aerobacter, Agribacterium, Azotobacter, Spirilla, Serratia, Vibrio, Rhizobium, Chlamydia, Rickettsia, Trepanema, and Fusobacterium,

DETDESC:

DETD(23)

Enzymes . . . dapC, dapD, and dapE genes. Another enzyme which exemplifies one of this type, i.e., is essential for DAP synthesis, is **aspartate** semi-aldehyde **dehydrogenase** (ASD), which is encoded in the asd gene.

DETDESC:

DETD(43)

Once . . . described supra, including non-pathogenicity, are

contemplated by this invention, including but not limited to Salmonella, E. coli --S. typhimurium hybrids, **Shigella**, Yersinia, Pasteurella, Legionella or Brucella. Preferred microbes are members of the genus Salmonella such as S. typhimurium, S. typhi, S.. . .

DETDESC:

DETD(45)

It . . . Bordetella pertussis, Mycobacterium tuberculosis, Mycobacterium leprae, Bordetella avium, Escherichia coli, Streptococcus equi, Streptococcus pneumoniae, Brucella abortus, Pasteurella hemolytica, Vibrio cholera, **Shigella** species, and Legionella pneumophila are additional examples of bacteria within the scope of this invention from which genes could be. . .

=> d 3 ab

US PAT NO: 5,387,744 :IMAGE AVAILABLE: L8: 3 of 4

ABSTRACT:
This invention provides immunogenic compositions for the immunization of a vertebrate or invertebrate comprising an avirulent derivative of S. typhi. The derivatives having a mutation of the cya and/or crp and/or cdt genes. The invention also provides immunogenic compositions for the immunization of a vertebrate and invertebrate comprising an avirulent derivative of the above type which is capable of expressing a recombinant gene derived from a pathogen of said vertebrate or invertebrate individual to produce an antigen capable of inducing an immune response against said pathogen. Other embodiments of the invention include methods of preparing immunogenic compositions from these strains, and strains useful in the preparation of the immunogenic compositions, as well as methods of stimulating the immune system to respond to an immunogenic antigen of S. typhi by administration of the immunogenic composition.

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(FILE 'USPAT' ENTERED AT 16:55:37 ON 08 OCT 1997)
L1 1802 S SHIGELLA
L2 39731 S MAMMAL?
L3 92 S L1(P)L2
L4 348306 S ENTRY OR ENTER OR ENTERED
L5 1 S L4(P)L3
L6 104 S ASPARTATE(4A)DEHYDROGENASE
L7 0 S L1(P)L6
L8 4 S L1 AND L6

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